Fiscal Year:	FY 2016	**Task Last Updated:**	FY 12/04/2015
PI Name:	Deymier, Alix C. Ph.D.		
Project Title:	Effect of Unloading on the Structure and Mechanics of the Rotator Cuff Tendon-to-Bone Insertion		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Musculoskeletal Alterations Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Bone Fracture**:Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (2) **Osteo**:Risk Of Early Onset Osteoporosis Due To Spaceflight		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:	NOTE: Also known as Alix Deymier-Black; former affiliation Washington University School of Medicine (Ed., 3/8/17)		
Project Type:	GROUND	**Solicitation / Funding Source:**	2013 NSBRI-RFA-13-01 Postdoctoral Fellowships
Start Date:	11/01/2013	**End Date:**	10/31/2016
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date is now 10/31/2016 per NSBRI (Ed., 10/13/15)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Thomopoulos, Stavros (MENTOR/ Washington University)		
Grant/Contract No.:	NCC 9-58-PF03503		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	POSTDOCTORAL FELLOWSHIP The goal of this project is to investigate the effect of unloading on the tendon-to-bone attachment at a number of hierarchical scales. At the nanometer scale, I proposed to examine changes in the organization of the bone mineral relative to the collagen fibrils with unloading via Transmission electron microscopy-electron energy loss spectroscopy (TEM-EELS). At a scale on the order of micrometers, I was interested in employing Raman and high-energy nano-x-ray diffraction (XRD) to identify modifications made to the mineral content, composition, structure and organization in the interfacial tissue. Micro-mechanical testing would be employed to examine changes in the mechanics at the micron scale. At the millimeter scale. Micro-computed tomography (μCT) and tensile testing were employed to determine the effects of unloading on bone quantity and quality and tissue mechanics. In the past two years, significant discoveries have been made explaining how the structure and mechanics of the tendon-to-bone attachment vary with unloading. Botulinum Toxin A (Btx) injections into the supraspinatus muscle were employed as an Earthbound model of disuse and unloading. At the millimeter scale, I found that 3 weeks of unloading resulted in a ~30% loss in bone volume as measured by μCT. Surprisingly, this loss was accompanied by a significant increases in tendon elastic modulus. This change in modulus is likely due to a changes in the soft tissue composition during unloading or structural changes at lower hierarchical scales. The tendon-to-bone attachment exhibits a gradient in mineral content at the micrometer scale. The width of this mineral gradient remains unaffected by unloading. However, nano-XRD studies indicate that the gradient region exhibits a variety of changes in mineral organization and structure. Traversing from the unmineralized tendon to the mineralized bone, the mineral crystals exhibit increased size, alignment, and compressive strain in both control and unloaded samples. However, unloading results in greater misalignment of the mineral crystals and smaller crystal sizes. Inputting these changes in crystal size and alignment into a basic rotational model it was determined that unloading leads to a decrease in work of rotation with unloading, leading to a decrease in tissue toughness. Raman measurements of the mineralized tissues showed that the mineral composition is modified due to unloading resulting in a decrease in carbonate substitution in the mineral structure. Together these results show that the effects of unloading are not limited to a single hierarchical scale but affect the interfacial tissue at a number of length scales. By understanding what structural and mechanical features are modified by unloading we can better focus our efforts when developing strategies for injury prevention and repair. For the next year, I will continue to examine the structure and mechanics across the length scales. I have established a collaboration with Prof. Anthony Lau at the College of New Jersey examining the structural efficiency of the bone architecture. Comparing Btx treated samples to space flight samples will serve to validate Btx treatment as a microgravity analogue. To better understand the increased modulus of the tendon-to-bone attachment I am also undertaking a study examining changes to the failure mode and failure area with unloading. Finally, at the nano-meter scale, we have preliminary evidence that mineral crystals are located both within and on the surface of collagen fibrils in regions of high mineralization but become uniquely extra-fibrillar with decreased mineralization. Samples have been embedded and sectioned to perform a full study examining nano-scale mineral distribution via TEM-EELS. I believe that we will see a decrease in extra-fibrillar mineral with unloading which would help explain the decrease in crystal size seen by XRD.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Rotator cuff tears are extremely prevalent, especially in the elderly population (~50% prevalence in individuals over 80 years). Even in the best of situations these tears are difficult to repair with a failure rate for repaired rotator cuffs as high as 94%. Rotator cuff tears tend to occur at the interface between tendon and bone. Such interfaces between dissimilar materials are prone to stress concentrations and increased failure risk. In healthy tissue, a number of structural mechanisms such as gradients in mineral content, collagen orientation, and matrix composition serve to dissipate these stress concentrations. The increased occurrence of rotator cuff injuries in the elderly population suggests that there may be changes in the interfacial structure due to unloading as a result of disuse or decreased use of the shoulder. Understanding how changes in the enthesis structure affect the mechanics of the insertion in loaded and unloaded systems will help us to develop enhanced techniques for treatment and repair. Therefore, the research performed in this project will not only help the astronaut population, but will also provide essential information in regards to the mechanics of rotator cuff tissues and how they respond to use and disuse.
Task Progress:	This project focuses on examining the mechanical and structural changes induced in the tendon-to-bone attachment during unloading at multiple length scales. This includes examining the tensile mechanics and bone structure at the millimeter scale, the micro-mechanics and mineral organization, composition and structure at the micrometer scale, and the mineral organization relative to the collagen at the nano-meter scale. In the past year I have focused specifically on changes to the attachment at the millimeter and micrometer scales. In all cases, I employed injections of Botulinum Toxin A (Btx) in the supraspinatus muscle, which induces local paralysis, as an analogue for unloading and microgravity. Significant bone loss due to unloading was measured via μCT. Tensile testing of the loaded and unloaded samples indicated that there is a significant increase in the attachment modulus. Further work to explain this increase in stiffness by examining failure modes and failure area is currently underway. At the micrometer scale, I was interested in examining the gradient region of the tendon to bone attachment where the composition transitions from fully mineralized to unmineralized. X-ray fluorescence and Raman spectroscopy results both indicate that there is no change in the width of this graded region with unloading. However, the composition, structure, and organization of the mineral crystals in the graded region is modified. Nano-X-ray diffraction measurements performed across the graded region show that trends in the mineral size, orientation and stiffness are the same for loaded and unloaded samples. Moving from the unmineralized to mineralized regions of the attachment the crystal size, compressive residual strain, and crystal alignment increase. However, the unloaded samples exhibit greater misalignment and decreased crystal size. Rotational models showed that these changes induced by unloading resulted in a decreased work of rotation upon loading suggesting a decrease in toughness. At the nanometer scale, Transmission Electron Microscopy–Electron Energy Loss Spectroscopy (TEM-EELS) has been used to examine the location of mineral crystals relative to the collagen fibrils in healthy tendon-to-bone attachments. I intend to pursue this preliminary study to understand how unloading modifies the nano-structure of the tendon-to-bone attachment. Together, the results gathered in the past year provide important information in understanding what features of the tendon-to-bone attachment are affected by unloading. This understanding will allow us to better focus our efforts when developing strategies for reducing rotator cuff tears and other musculoskeletal injuries.

Bibliography Type:	Description: (Last Updated: 10/19/2020)
Abstracts for Journals and Proceedings	Deymier-Black AC, Schwartz AG, Cai Z, Genin GM, Thomopoulos S. "Role of Mineral Organization on the Mechanics of the Tendon-To-Bone Interface Examined via High Energy X-Ray Diffraction." 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. , Jan-2015
Abstracts for Journals and Proceedings	Deymier-Black AC, Schwartz AG, Cai Z, Genin GM, Thomopoulos S. "Effect of Unloading on the Organization of Mineral Crystals at the Tendon-to-Bone Attachment." Musculoskeletal Research Center Winter Symposium, St Louis, MO, Feb 16, 2015. Musculoskeletal Research Center Winter Symposium, St Louis, MO, Feb 16, 2015. , Feb-2015
Articles in Peer-reviewed Journals	Deymier-Black AC, Pasteris JD, Genin GM, Thomopoulos S. "Allometry of the tendon enthesis: Mechanisms of load transfer between tendon and bone." Journal of Biomechanical Engineering. 2015 Nov;137(11):111005. http://dx.doi.org/10.1115/1.4031571 ; PubMed PMID: 26355607 , Nov-2015
Awards	Deymier-Black A. "Musculoskeletal Research Center Winter Symposium Poster Award, February 2015." Feb-2015
Awards	Deymier-Black A. "NSBRI Dr. David Watson Poster Contest Award, January 2015." Jan-2015
Papers from Meeting Proceedings	Deymier-Black AC, An Y, Schwartz AG, Genin GM, Thomopoulos S, Barber AH. "Micrometer Scale Mechanical Properties of the Tendon-to-Bone Attachment." SB3C. Summer Biomechanics, Bioengineering and Biotransport Conference, Snowbird, Utah, June 17-20, 2015. Proceedings of the 2015 Summer Biomechanics, Bioengineering and Biotransport Conference. Paper number SB3C2015-594. , Jun-2015